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<b>TRANSMITTAL FORM</b>  (to be used for all correspondence after initial filing)	Application Number	10/760,091	
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	First Named Inventor	Thomas L. CANTOR	
	Art Unit	1641	
	Examiner Name	C. Cheu	
Total Number of Pages in This Submission	30	Attorney Docket Number	532212000624

ENCLOSURES (Check all that apply)		
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Printed name	Peng Chen		
Date	July 26, 2006	Reg. No.	43,543

I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail, in an envelope addressed to: MS Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.	
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Docket No.: 532212000624  
(PATENT)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of:  
Thomas L. CANTOR et al.

Application No.: 10/760,091

Confirmation No.: 2110

Filed: January 16, 2004

Art Unit: 1641

For: METHODS FOR DIFFERENTIATING AND  
MONITORING PARATHYROID AND BONE  
STATUS RELATED DISEASES

Examiner: C. Cheu

**RESPONSE TO RESTRICTION REQUIREMENT**

MS Amendment  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Dear Sir:

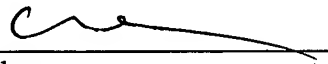
In response to the restriction requirement set forth in the Office Action mailed June 26, 2006, Applicant attaches a copy of the Preliminary Amendment (excluding exhibits) which was filed with the subject application on January 16, 2004. The Preliminary Amendment cancels claims 1-46 and adds claims 47-107. Therefore, the currently pending claims are 47-107.

Applicants respectfully request the Examiner withdraw the current restriction requirement and examine the currently pending claims on the merits.

In the unlikely event that the transmittal form is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing 532212000624. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: July 26, 2006

Respectfully submitted,

By   
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PATENT  
Docket No. 532212000624

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*Judy Bridgewater*  
Judy Bridgewater

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In the application of:

Thomas L. CANTOR

Serial No.: Continuation of U.S. Application  
No. 09/344,639

Filing Date: Herewith

For: METHODS FOR DIFFERENTIATING  
AND MONITORING PARATHYROID  
AND BONE STATUS RELATED  
DISEASES

Examiner: To Be Assigned

Group Art Unit: To Be Assigned

**PRELIMINARY AMENDMENT**

Mail Stop Patent Application  
Commissioner for Patents  
P O Box 1450  
Alexandria, VA 22313-1450

Dear Sir:

Prior to examination of the above-referenced application, please amend the application as follows. Enclosed are the following exhibits:

Exhibit A: US 2003/0082179 A1 (U.S. Application No. 09/898,398);

- Exhibit B: U.S. Patent Application No. 09/231,422, filed on January 14, 1999;
- Exhibit C: U.S. Patent Application No. 09/344,639, filed on June 26, 1999
- Exhibit D: Gao et al., *Clinica Chimica Acta* 245 (1996) 39-59;
- Exhibit E: J.S. McMurray, *Biopolymers* 47(5):405-11 (1998) (abstract); and
- Exhibit F: T. Yasuda, H. Niimi, *Acta Paediatr Jpn.* Aug;39(4):485-90 (1997) (abstract).

## AMENDMENTS

### In the specification:

The paragraph, beginning at page 1, line 20 has been amended as follows:

The present application is a continuation of U.S. Patent Application No. 09/344,639, filed on June 26, 1999, now allowed; which is a continuation-in-part of a non-provisional utility patent application filed in the United States Patent and Trademark Office, Serial Number U.S. Patent Application No. 08 09/231,422, filed on January 14, 1999, now allowed.

The paragraph, beginning at page 8, line 7 has been amended as follows:

FIGURES 6A and 6B is-a are diagrammatic views showing binding of whole (1-84) PTH compared with interference from PIN non (1-84) PTH fragments (e.g., (7-84) PTH (SEQ ID NO:6)) in conventional I-PTH assays.

The paragraph, beginning at page 11, line 7 has been amended as follows:

In order to make the signal antibody in the above assay, first one makes a synthetic PTH peptide corresponding either to hPTH (Ser -Val -Ser -Glu -Ile -GIn -Leu -Met) (SEQ ID NO:4), rat PTH (Ala -Val- Ser -Glu -Ile -GIn -Leu -Met) (SEQ ID NO:7), or at least four amino acids in the common sequence. The selected peptide can play two roles in making an assay, first as a specific source for creating a polyclonal antibody or monoclonal antibody source for signal antibody or capture antibody, and second as part of an affinity purification means for isolating the desired signal antibody or capture antibody.

At page 12, please amend the paragraph of lines 8-22 as follows:

To create an affinity-purified ~~anti-(1-6)~~ anti-(1-6) PTH antibody, one first uses a selected initial PTH sequence peptide as described above as part of an immunogen for injection into a goat. The peptide can be used either by itself as an injectable immunogen, incorporated into a non PTH peptide having a molecular weight, typically, of between about 5,000 and 10,000,000, or as part of the wPTH complete sequence. The ~~immunogen~~ immunogen is mixed with an equal volume of Freund's complete adjuvant which is a mixture of light mineral oil, Arlacel detergent, and inactivated mycobacterium tuberculosis bacilli. The resulting mixture is homogenized to produce an aqueous/oil emulsion which is injected into the animal (typically a goat) for the primary immunization. The immunogen dose is approximately 50-400 micrograms. The goats are injected monthly with the same dose of immunogen complex except no mycobacterium tuberculosis bacilli is used in these subsequent injections. The goats are bled monthly, approximately three months after the 20 primary immunization. The serum (or antiserum) is derived from each bleeding by separating the red blood cells from the blood by centrifugation and removing the antiserum which is rich in (1-6) PTH antibodies.

The paragraph, beginning at page 13, line 16 has been amended as follows:

FIGURE 5 shows the results for 34 normal human serum samples from healthy subjects which were assayed both by the present wPTH IRMA and the above I-PTH assay. In every case, the level of wPTH detected by the IRMA is lower than that reported by the I-PTH assay, demonstrating the ability of the present IRMA to avoid detecting the interfering large, non (1-84) PTH fragments detected by the I-PTH assay. FIGURES 6A and 6B illustrate[s] how such interference can occur. An N-terminal PTH specific signal antibody which is not specific to the initial PTH peptide sequence, as in the present invention, can detect not only wPTH (as in the

~~upper part of~~ FIGURE 6A), but also can detect large, non (1-84) PTH fragments (as in ~~the lower~~  
~~part of~~ FIGURE 6B).



**In the claims:**

This listing of claims will replace all prior versions, and listings, of claims in the application:

Claims 1-46 (Canceled).

47. (New) A method for producing antibodies to a three-dimensional epitope of a bioactive human parathyroid hormone, comprising:

- a) immunizing an animal with the bioactive human parathyroid hormone; and
- b) recovering antibodies from the animal; whereby the antibodies specifically recognize the three-dimensional structure of the bioactive human parathyroid hormone.

48. (New) The method of claim 47, further comprising immunizing the animal with the human parathyroid hormone a second time before recovering the antibodies from the animal.

49. (New) The method of claim 47, wherein the human parathyroid hormone is coupled to a carrier.

50. (New) The method of claim 49, wherein the carrier is keyhole limpet hemocyanin.

51. (New) The method of claim 47, wherein the bioactive human parathyroid hormone comprises SEQ ID NO: 1:

52. (New) The method of claim 47, further comprising isolating the antibodies.

53. (New) The method of claim 52, wherein the antibodies are isolated by affinity chromatography.

54. (New) The method of claim 53, wherein the antibodies are isolated by screening the antibodies with fragments of the human parathyroid hormone linked to a solid phase.

55. (New) A method for producing antibodies that recognize and bind the bioactive, three-dimensional epitope of parathyroid hormone, comprising

- a) immunizing an animal with parathyroid hormone;
- b) immunizing the animal with parathyroid hormone a second time; and
- c) recovering the antibodies from the animal,

whereby the antibodies recognize and bind the bioactive, three-dimensional epitope of parathyroid hormone.

56. (New) The method of claim 55, wherein the parathyroid hormone is conjugated to a carrier.

57. (New) The method of claim 56, wherein the carrier is keyhole limpet hemocyanin.

58. (New) The method of claim 54, wherein the parathyroid hormone is human parathyroid hormone.

59. (New) The method of claim 55, further comprising isolating the antibodies so recovered.

60. (New) The method of claim 59, wherein the antibodies are isolated by affinity chromatography.

61. (New) The method of claim 60, wherein the antibodies are isolated by fragments of parathyroid hormone coupled to a solid phase.

62. (New) The method of claim 61, wherein the fragments of parathyroid hormone are selected from the group consisting of amino acids 1-13, 13-34, and 39-84 of SEQ ID NO: 1.

63. (New) The method of claim 61, wherein the antibodies are isolated by a fragment of parathyroid hormone consisting of amino acids 1-13 of SEQ ID NO: 1.

64. (New) A method for producing antibodies that recognize and bind the bioactive, three-dimensional epitope of parathyroid hormone, comprising

a) immunizing an animal with parathyroid hormone, wherein the parathyroid hormone comprises amino acids 1-84 of SEQ ID NO: 1;

b) immunizing the animal with parathyroid hormone a second time; and

c) recovering the antibodies from the animal,

whereby the antibodies recognize and bind the bioactive, three-dimensional epitope of parathyroid hormone.

65. (New) The method of claim 64, further comprising isolating the antibodies so recovered.

66. (New) The method of claim 64, wherein the bioactive three-dimensional epitope of parathyroid hormone consists of amino acids 1-13 of SEQ ID NO: 1.

67. (New) A method for producing antibodies that recognize and bind the bioactive, three-dimensional amino terminus of parathyroid hormone, comprising

a) immunizing an animal with parathyroid hormone conjugated to a keyhole limpet hemocyanin, wherein the parathyroid hormone comprises amino acids 1-84 of SEQ ID NO: 1;

b) subsequently immunizing the animal with parathyroid hormone; and

c) recovering the antibodies from the animal,

whereby the antibodies recognize and bind the bioactive, three-dimensional amino terminus of parathyroid hormone.

68. (New) The method of claim 67, wherein the bioactive three-dimensional amino terminus of parathyroid hormone consists of amino acids 1-13 of SEQ ID NO: 1.

69. (New) An isolated antibody that recognizes and binds the bioactive, three-dimensional epitope of parathyroid hormone.

70. (New) The isolated antibody of claim 69, wherein the bioactive, three dimensional epitope is the amino terminus of parathyroid hormone.

71. (New) The isolated antibody of claim 69, wherein the parathyroid hormone is human parathyroid hormone.

72. (New) The isolated antibody of claim 69, wherein the bioactive, three-dimensional epitope consists of amino acids 1-13 of SEQ ID NO: 1.

73. (New) An isolated antibody recognizing a peptide comprising an amino acid sequence from Ser in the 1 position to Lys in the 13 position of SEQ ID NO: 1.

74. (New) An isolated antibody according to claim 73 recognizing a peptide consisting of an amino acid sequence from Ser in the 1 position to Lys in the 13 position of SEQ ID NO: 1.

75. (New) An antibody that is immunoreactive with the bioactive amino-terminal portion of human parathyroid hormone.

76. (New) The antibody of claim 75, wherein the bioactive amino-terminal portion comprises amino acids 1-13 of SEQ ID NO: 1.

77. (New) The antibody of claim 75, wherein the bioactive amino-terminal portion consists of amino acids 1-13 of SEQ ID NO: 1.

78. (New) A therapeutic composition comprising the antibody of claim 75, and a pharmaceutically-acceptable carrier.

79. (New) The antibody of claim 75, wherein the antibody reduces adenylate cyclase activity by binding to the bioactive portion of the parathyroid hormone.

80. (New) Any one of the antibodies of claims 69, wherein the antibody is a polyclonal antibody.

81. (New) Any one of the antibodies of claims 69, wherein the antibody is a monoclonal antibody.

82. (New) Any one of the antibodies of claims 69, wherein the antibody is a humanized antibody.

83. (New) Any one of the antibodies of claims 69, wherein the antibody is an antibody fragment.

84. (New) Any one of the antibodies of claims 69 coupled to a detectable marker.

85. (New) An antibody that specifically binds to the bioactive three-dimensional epitope of human parathyroid hormone, wherein the epitope consists of amino acids 1-13 of SEQ ID NO: 1.

86. (New) A polyclonal antibody that recognizes and binds the bioactive three-dimensional epitope of human parathyroid hormone produced by a process comprising the following steps:

a) immunizing an animal with human parathyroid hormone linked with keyhole limpet hemocyanin;

b) immunizing the animal with human parathyroid hormone; and

c) recovering the antibodies from the animal,

whereby the antibodies recognize and bind the bioactive three-dimensional epitope of human parathyroid hormone.

87. (New) A polyclonal antibody that recognizes and binds the bioactive three-dimensional epitope of human parathyroid hormone produced by a process comprising the following steps:

a) immunizing an animal with human parathyroid hormone linked with keyhole limpet hemocyanin;

b) immunizing the animal with human parathyroid hormone; and

c) recovering the antibodies from the animal,

whereby the antibodies recognize and bind the bioactive three-dimensional epitope of human parathyroid hormone, and wherein the bioactive three-dimensional epitope consists of amino acids 1-13 of SEQ ID NO: 1.

88. (New) An antibody selective for bioactive parathyroid hormone.
89. (New) An antibody selective for bioactive parathyroid hormone, wherein the antibody recognizes and binds at least one of the first thirteen amino acids of SEQ ID NO: 1.
90. (New) An isolated antibody that recognizes and binds the bioactive, three-dimensional epitope of parathyroid hormone, or a variant thereof.
91. (New) An isolated antibody that recognizes and binds the bioactive, three-dimensional epitope of parathyroid hormone, or a fragment thereof.
92. (New) A kit comprising an antibody that recognizes and binds the bioactive, three-dimensional epitope of parathyroid hormone.
93. (New) The kit of claim 92, wherein the antibody is coupled with a detectable label.
94. (New) The kit of claim 92, wherein the bioactive, three-dimensional epitope consists of amino acids 1-13 of SEQ ID NO: 1.
95. (New) The kit of claim 92, further comprising tools for obtaining a biological sample containing parathyroid hormone from a patient.



96. (New) The kit of claim 93, wherein the detectable label is selected from the group consisting of chemiluminescent markers, fluorescent markers, radioactive markers, and enzymatic markers.

97. (New) The kit of claim 93, wherein the detectable label is an acridinium ester.

98. (New) A method for detecting bioactive parathyroid hormone in a sample, comprising

a) exposing the sample to an antibody that recognizes and binds the bioactive three-dimensional epitope of parathyroid hormone; and

b) detecting the antibody-hormone complex, thereby detecting the bioactive parathyroid hormone in the sample.

99. (New) The method of claim 98, wherein the antibody that recognizes and binds the bioactive three-dimensional epitope of parathyroid hormone is coupled with a detectable marker.

100. (New) The method of claim 98, further comprising exposing the antibody-hormone complex to another antibody that recognizes and binds parathyroid hormone before step (b).

101. (New) A method for detecting bioactive parathyroid hormone in a sample, comprising

a) exposing the sample to a capture antibody that recognizes and binds the bioactive three-dimensional epitope of parathyroid hormone;

b) exposing the capture antibody-hormone complex to a detection antibody that binds a different epitope than the capture antibody; and

b) detecting the antibody-hormone complex,

thereby detecting the bioactive parathyroid hormone in the sample.

102. (New) The method of claim 101, wherein the detection antibody is coupled to a chemiluminescent marker.

103. (New) The method of claim 102, wherein the chemiluminescent marker is an acridinium ester.

104. (New) The method of claim 98, wherein the sample is from a patient with hyperparathyroidism or hypoparathyroidism.

105. (New) The method of claim 101, wherein the sample is from a patient with hyperparathyroidism or hypoparathyroidism.

106. (New) An immunoassay comprising an antibody that recognizes and binds the bioactive three-dimensional amino terminus of human parathyroid hormone.

107. (New) The immunoassay of claim 106, wherein the bioactive three-dimensional amino terminus consists of amino acids 1-13 of SEQ ID NO: 1.

**REMARKS**

New claims 47-107 are added to provoke interference with claims 1-61 of U.S. Application No. 09/898,398, published as U.S. publication number US 2003/0082179 A1 (Exhibit A) on May 1, 2003 under 37 C.F.R. §1.604.

New claims 47-107 are fully supported by the specification and claims as originally filed. As will be appreciated by the Office, support for all newly added claims may be found throughout the specification as an entirety, including the examples, figures and claims. No new matter has been added, and entry of the amendment is respectfully requested.

**Support for new claims 47-54**

For example, support for claims 47 and 51 can be found, *inter alia*, at page 11, 2nd paragraph to page 13, 1st paragraph, which teaches the use of an initial PTH sequence in itself or as “part of the wPTH complete sequence,” to generate an “anti-(1-8) PTH antibody.” *See also* page 3, lines 17-23, which discloses the teaching of Gao et al., *Clinica Chimica Acta* 245 (1996) 39-59 (the Gao article) (Exhibit D), and page, lines 27-28, which states that all publications or unpublished patent applications mentioned in the '639 Application are hereby incorporated by reference. *See* page 4, lines 13-19 and page 20, lines 13-14 of the '639 application (see also page 3, lines 17-23; and page 10, lines 27-28). Accordingly, the teachings of the Gao article are incorporated by reference in the present application. The Gao article teaches numerous human PTH peptides, including hPTH<sub>1-34</sub>, hPTH<sub>1-38</sub> (*See* the Gao article at page 41), hPTH<sub>1-33</sub>, hPTH<sub>1-36</sub>, hPTH<sub>1-37</sub> (*See* the Gao article at page 54), and the use of hPTH<sub>1-38</sub> in generating anti-hPTH antibodies (*See* the Gao article at page 41). Support can be found, *inter alia*, at page 12, lines 12-22 of the present application, which teaches initial immunization, and obtaining antiserum at the end of the immunization process (*See also* page 8, line 28 to page 9, line 7 of the '422 application). Page 12, line 24 through page 13, line 4 of the present application teaches purifying anti-PTH antibody from the antiserum (*See also* page 9, lines 9-18 of the '422 application).

As explained in US 2003/0082179, “PTH is considered to be bioactive when the polypeptide is able to regulate adenylate cyclase activity.” *See* page 3, paragraph 39. At page 2, lines 7-10 of the present specification it is indicated that the domain for adenylate cyclase activation comprises amino acid residues 1 to 7. The present specification clearly provides a method for producing antibodies that recognize a variety of PTH peptide fragments ranging from, PTH<sub>1-7</sub> up to PTH<sub>1-84</sub>, and a variety of N-terminal peptide fragments comprising the domain for adenylate cyclase activation. *See, e.g.*, page 11, line 7 to page 13, line 4 (*See* also page 8, line 24 to page 9, line 18 of the ‘422 application). US 2003/0082179 also indicates that a “bioactive human parathyroid hormone” includes hPTH (1-13), hPTH (1-34) and hPTH (1-84). *See* paragraph 39 of US 2003/0082179. As discussed above, the present specification teaches the step of immunizing an animal, *e.g.*, a goat, with the bioactive human parathyroid hormone such as hPTH (1-84).

What constitutes “a three-dimensional epitope of a bioactive human parathyroid hormone” is not defined in US 2003/0082179. However, US 2003/0082179 states “[i]n a preferred embodiment, the antibody recognizes and binds an epitope within the first seven amino acids of PTH, or hPTH.” *See* paragraph 61 of US 2003/0082179. Accordingly, the “three-dimensional epitope of a bioactive human parathyroid hormone” includes an epitope within the first seven amino acids of PTH, or hPTH. As discussed above, the present specification teaches a method for generating “anti-(1-8) PTH antibody,” which would inherently include an epitope within the first seven amino acids of PTH, or hPTH. In addition, the present specification teaches generating, recovering and isolating antibodies that specifically recognize adenylate cyclase active or “bioactive” PTH peptides. Since a bioactive PTH, *e.g.*, hPTH (1-84), presumably contains its correct three-dimensional structure, the methods taught in the present application provide methods for producing antibodies that inherently specifically recognize the three-dimensional structure of a bioactive human PTH.

Support for claim 48 can be found, *inter alia*, at page 12, lines 8-22 of the present specification, which teaches repeated administration of immunogen to generate antibodies thereto (*See also* page 8, line 24 to page 9, line 7 of the '422 application).

Support for claims 49 and 50 can be found, *inter alia*, at page 12, lines 8-22 of the present specification, which teaches that the immunogen can be coupled to a carrier such as a larger peptide that typically can have a molecular weight encompassing that of keyhole limpet hemocyanin (KLH), *i.e.*, between about 5000 and 10,000,000 (*See also* page 8, line 24 to page 9, line 7 of the '422 application). Although the use of KLH is not explicitly stated in the present specification, it is routinely utilized in the art as a target peptide carrier for immunization protocols at the time the present priority applications were filed (U.S. Patent Application No. 09/344,639, June 26, 1999, and U.S. Patent Application No. 09/231,422, January 14, 1999). *See, e.g.*, J.S. McMurray, *Biopolymers* 47(5):405-11 (1998) (abstract) (Exhibit E).

Support for claims 52-54 can be found, *inter alia*, at page 12, line 8 to page 13, line 4 of the present specification (*See also* page 8, line 24 to page 9, line 18 of the '422 application).

#### **Support for new claims 55-63**

Compared to claim 47, claim 55 have two differences. First, any parathyroid hormone, not just bioactive human parathyroid hormone, can be used in the immunization step. Second, claim 55 requires a second immunization step. These differences are taught in the present specification. For example, the use of PTH from various animals in addition to hPTH is taught at page 9, lines 4-11 and page 10, lines 4-14 of the present specification. The second immunization step is also taught. *See* the above discussion for claim 48. Claims 56-61 are supported by the present specification. *See* the above discussion for claims 49-54.

Support for claims 62 and 63 can be found, *inter alia*, at page 10, lines 16-20; page 11, line 7 to page 13, line 4 of the present specification (*See also* page 7, lines 6-10; page 8, line 24 to page 8, line 7 of the '422 application) which teaches the use of PTH fragments to isolate PTH

antibodies. Support for claims 62 and 63 lies in the fact that claims 62 and 63 of the present application use a genus of PTH peptides for the affinity purification step. The shortest PTH peptide in the genus is human PTH<sub>1-8</sub> and the longest PTH peptide in the genus is human PTH<sub>1-34</sub>. There are only 26 species in the genus, *i.e.*, PTH<sub>1-8</sub>, PTH<sub>1-9</sub>, PTH<sub>1-10</sub>, . . . PTH<sub>1-34</sub>. Under this circumstance, the genus comprising PTH<sub>1-13</sub> disclosed in claims 62 and 63 of the present application provides for a description of a species within the genus. *See Union Oil of Cal. v. Atlantic Richfield Co.*, 208 F.3d 989, 997, 54 USPQ2d 1227, 1232-33 (Fed. Cir. 2000) (Description in terms of ranges of chemical properties which work in combination with ranges of other chemical properties to produce an automotive gasoline that reduces emissions was found to provide an adequate written description of [chemical components within the disclosed ranges] even though the exact chemical components of each combination were not disclosed and the specification did not disclose any distinct embodiments corresponding to any claim at issue. “[T]he Patent Act and this court’s case law require only sufficient description to show one of skill in the . . . art that the inventor possessed the claimed invention at the time of filing.”).

As for the PTH fragment comprising PTH<sub>13-34</sub> (in claim 62), support can be found in the present specification at page 6, line 20 to page 7, line 3, which teaches the use of an antibody that specifically detects cyclase inactive PTH (CIP) fragments comprising a specific portion of PTH<sub>7-38</sub>, and preferably a specific portion of PTH<sub>9-34</sub>. Similar to the N-terminal PTH fragments set out above, PTH<sub>13-34</sub> comprises a species within this genus. *See supra*. And, as for the PTH fragment comprising PTH<sub>39-84</sub> (in claim 62), support can be found in the present specification at page 10, lines 16-20, which teaches the use of an antibody that specifically detects C-terminal PTH fragments comprising a specific portion of PTH<sub>39-84</sub>.

#### **Support for new claims 64-68**

Compared to claim 55, the only difference in claim 64 is that claim 64 requires the use of 1-84 of SEQ ID NO: 1, *i.e.*, hPTH (1-84), in the immunization step. The use of hPTH (1-84) in the immunization step is taught in the present specification. For example, at page 11, 2nd

paragraph to page 13, 1st paragraph, the present specification teaches the use of an initial PTH sequence in itself or as “part of the wPTH complete sequence,” to generate an “anti-(1-8) PTH antibody.” The present specification supports claims 65 and 66 for the same reason that it supports claims 59 and 63 as discussed above.

The only difference between claims 64 and 67 is that claim 67 uses KLH as a carrier. As discussed above in connection with claims 49 and 50, at page 12, lines 8-22, the present specification teaches that the immunogen can be coupled to a carrier such as a larger peptide that typically can have a molecular weight encompassing that of keyhole limpet hemocyanin (KLH), *i.e.*, between about 5,000 and 10,000,000 (*see also* page 8, line 24 to page 9, line 7 of the ‘422 application). Although the use of KLH is not explicitly stated in the present specification, it is routinely utilized in the art as a target peptide carrier for immunization protocols at the time the present priority applications were filed. The present specification supports claim 69 for the same reason that it supports claim 63 as discussed above.

**Support for new claims 69-91**

Support for claims 69-85 and 88-91 can be found, *inter alia*, at page 12, line 8 to page 13, line 4 (*See also* page 8, line 24 to page 9, line 7). The present specification teaches antibodies that inherently recognize and bind, and/or specifically bind, the bioactive, three-dimensional epitope of PTH. *See* the above discussion for claim 47. Such antibodies are selective for bioactive PTH. In a particular embodiment, the antibodies are inherently capable of recognizing and binding the three-dimensional epitope of PTH comprising the amino terminus, and/or PTH<sub>1-13</sub>. The PTH protein can be a human PTH protein. SEQ ID NO: 1 sets out a peptide sequence having Ser in position 1 and Lys in position 13, and it would be obvious to produce antibodies to this segment of PTH based on the present disclosure. The term “immunoreactive” provides another term for binding of an antibody to an antigen, thus the present specification teaches antibodies that are immunoreactive with the bioactive amino-terminal portion of human PTH, and antibodies that are immunoreactive with PTH<sub>1-13</sub>. The present specification further teaches



both polyclonal and monoclonal antibodies, and coupling these antibodies with detectable markers. And, although the present specification does not specifically teach the use of a pharmaceutically acceptable carrier with the described PTH antibodies, it would have been obvious to one of skill in the art to provide such a combination based on the present disclosure. Moreover, although the present specification does not specifically describe that the present antibodies reduce adenylate cyclase activity by binding the bioactive portion of PTH, such functionality comprises an inherent characteristic of the antibodies taught in the present specification.

Support for claim 86 can be found, *inter alia*, at page 11, line 7 to page 13, line 4 of the present specification (See also page 8, line 24 to page 9, line 18 of the '422 application), which teaches initial immunization together with a booster immunization to generate antibodies to PTH antigen, and thereafter recovering the antibodies. See also, page 12, lines 8-22 of the present specification, which teaches that the immunogen can be coupled to a carrier such as a larger peptide that typically can have a molecular weight encompassing that of keyhole limpet hemocyanin (KLH); *i.e.*, between about 5,000 and 10,000,000 (see also page 8, line 24 to page 9, line 7 of the '422 application). As indicated above, KLH was routinely utilized in the art as a target peptide carrier for immunization protocols at the time the presently claimed priority applications were filed.

The present specification teaches immunization with PTH coupled to a protein carrier, together with a second booster immunization to generate antibodies to the PTH antigen, and thereafter recovering the antibodies. As indicated above, these antibodies inherently recognize and bind the bioactive, three-dimensional epitope of PTH.

Support for claim 87 can be found, *inter alia*, at page 11, line 7 to page 13, line 4 of the present specification (See also page 8, line 24 to page 9, line 18 of the '422 application), which teaches initial immunization together with a booster immunization to generate antibodies to PTH antigen, and thereafter recovering the antibodies. See also, page 12, lines 8-22 of the present

specification, which teaches that the immunogen can be coupled to a carrier such as a larger peptide that typically can have a molecular weight encompassing that of keyhole limpet hemocyanin (KLH), *i.e.*, between about 5,000 and 10,000,000 (*see also* page 8, line 24 to page 9, line 7 of the '422 application). As indicated above, KLH was routinely utilized in the art as a target peptide carrier for immunization protocols at the time the presently claimed priority applications were filed.

The present specification teaches immunization with whole PTH coupled to a protein carrier, together with a second booster immunization to generate antibodies to the PTH antigen, and thereafter recovering the antibodies. As indicated above, the present specification teaches a method for producing and recovering antibodies that inherently recognize and bind the bioactive, three-dimensional epitope of PTH comprising PTH<sub>1-13</sub>. *See supra*.

**Support for new claims 92-97**

Support for claim 92-97 can be found, *inter alia*, at page 6, lines 5-8; page 9, line 14 to page 13, line 4 of the present specification (*See also* page 4, lines 11-14; page 6, line 5 to page 9, line 18 in the '422 application). As indicated above, the present specification teaches antibodies that inherently recognize and bind the bioactive, three-dimensional epitope of PTH comprising PTH<sub>1-13</sub>. Although kits are not specifically listed in the present application, general PTH assays containing PTH specific antibodies are provided. All components necessary for practicing the PTH assays taught in the present application are provided and one of skill in the art would understand that a kit comprising these components would be obvious and desired based on the present disclosure. As for tools to acquire a biological sample, such tools are standard in the art and inherently necessary to obtain a sample to practice the present methods. Moreover, although an acridinium ester is not specifically provided in the present disclosure, it provides one exemplary chemiluminescent agent that is well known in the art. The use of such a detectable label would be obvious in light of the present disclosure.

**Support for new claims 98-107**

Support for claims 98-100, 103-105 can be found, *inter alia*, at page 2, lines 21-26; page 4, line 24 page 5, line 9; page 9, line 14 to page 11, line 4 of the present specification (*See* also page 6, line 5 to page 7, line 23) which teaches a method for detecting cyclase active PTH by exposing a sample to an antibody that binds the cyclase activating epitope of PTH, and detecting the PTH/antibody complex. The antibody can also be labeled to aid in the detection. In addition, the present disclosure teaches the use of a second antibody to also bind the PTH peptide prior to detection of the antibody/PTH complex. Although hypoparathyroidism itself is not specifically exemplified, obtaining and measuring samples from patients having pseudohypoparathyroidism is exemplified. Notably, pseudohypoparathyroidism represents one form of hypoparathyroidism. *See, e.g.,* T. Yasuda, H. Niimi, *Acta Paediatr Jpn.* Aug;39(4):485-90 (1997) (abstract) (attached as Exhibit F).

Support for claims 101-105 can be found, *inter alia*, at page 2, lines 21-26; page 4, line 24 page 5, line 9; page 6, lines 5-10; page 9, line 14 to page 11, line 4 of the present specification (*See* also page 2, lines 2-14; page 4, lines 11-16; page 6, line 5 to page 7, line 23) which teaches a method for detecting cyclase active PTH by exposing a sample to a capture antibody that binds the cyclase activating epitope of PTH, exposing the sample to a second antibody that binds to different epitope than the capture antibody, and detecting the PTH/antibody complex. The detection antibody can also be coupled with a chemiluminescent marker to aid in the detection. Moreover, although an acridinium ester is not specifically provided in the present disclosure, it provides one exemplary chemiluminescent agent that is well known in the art. The use of such a detectable label would be obvious in light of the present disclosure. Although hypoparathyroidism itself not specifically exemplified, obtaining and measuring samples from patients having pseudohypoparathyroidism is exemplified. As indicated above, pseudohypoparathyroidism is one form of hypoparathyroidism.

Support for claims 106-107 can be found, *inter alia*, at page at page 11, line 8 to page 13, line 4 of the present specification (*See* also page 8, line 24 to page 9, line 7). Clearly, the present specification teaches immunoassays comprising antibodies that recognize and bind the bioactive amino terminus of PTH, even when that amino terminus comprises PTH<sub>1-13</sub>.

Accordingly, it is submitted that new claims 47-107 have support in the present application.

**Claims pending in U.S. Application No. 09/898,398 as of May 1, 2003**

U.S. Application No. 09/898,398 published on May 1, 2003. The current applicant appreciates that prosecution is ongoing in connection with U.S. Application No. 09/898,398 (the '398 application) such that the claim status therein is in a state of flux. In particular, the current applicant is aware that on September 10, 2001, the applicants in connection with the '398 application submitted a preliminary amendment. The substance of this September 10, 2001 amendment is unknown to the current applicant. Nevertheless, in order to preserve rights under 35 U.S.C. 135(2)(b), the current applicant has included claims directed to the same invention as that encompassed by the claims pending in the '398 application prior to the preliminary amendment of September 10, 2001. If the Office deems it appropriate under the circumstances, the current applicant would be receptive to the suggestion of claims directed to the same invention as that currently pending in the '398 application, if such claims have been amended from their state as they were prior to September 10, 2001.

**Proposed counts between claims 47-107 of the present application and pending claims of the '398 application**

Out of concern for easing the burden on the Patent Office, the Applicants set forth the proposed counts as comprising the independent claims. Notably all claims published in U.S. Application No. 09/898,398 (published as US 2003/0082179 A1) are identically copied herein.

The following table sets forth the counts and claims corresponding to the counts in both the present application and U.S. Application No. 09/898,398.

Count	Present claim number	U.S. Application No. 09/898,398 claim number
1	47	1
2	55	9
3	64	18
4	67	21
5	69	23
6	73	27
7	75	29
8	85	39
9	86	40
10	87	41
11	88	42
12	89	43
13	90	44
14	91	45
15	92	46
16	98	52
17	101	55
18	106	60

Accordingly, the present application is claiming the same invention as that set forth in U.S. Application No. 09/898,398.

### CONCLUSION

It is respectfully submitted that new claims 47-107 of the present application are fully supported by the specification and claims as originally filed and entry of new claims 47-107 is respectfully requested. It is further respectfully submitted that claims 47-107 of the present application and claims 1-61 of the '398 application are drawn to the same invention. It is respectfully requested that an interference be declared between claims 47-107 of the present application and claims 1-61 of the '398 application.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing 532212000624. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: January 16, 2004

Respectfully submitted,

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